Docket No.: 0701.100E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Redmon et al.	***Confirmation No.:***	4621
Serial No.:	10/082,685	***Group Art Unit:***	1617
Filed:	February 25, 2002	***Examiner:***	Travers, Russell S.
Title:	LACTOSE-FREE, NON-HYGROSCOPIC AND ANHYDROUS PHARMACEUTICAL COMPOSITIONS OF DESCARBOETHOXYLORATADINE		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Dear Sir:

I, Sharon M. Laughlin, hereby state and declare that:

1. I am a citizen of the United States of America and a resident of Hudson, Massachusetts;

2. I earned a B.S. in Pharmacy from University of Iowa College of Pharmacy in Iowa City, IA, in 1973, an M.S. degree in Pharmacy from University of Wisconsin School of Pharmacy in Madison, WI, in 1979, and a Ph.D. degree in Pharmacy from University of Wisconsin School of Pharmacy in Madison, WI, in 1983. My primary area of research, both academic and industrial has been in the preformulation and formulation of solid dosage pharmaceuticals. I am presently Director of Pharmaceutics Division at Sepracor, Inc. in Marlborough, Massachusetts. Prior to my employment at Sepracor, I was a Supervisor of Preformulation Group at Sanofi-Synthelabo Research in Malvern, Pensylvania, and worked in the area of pharmaceutical development at Pfizer in Groton, Connecticut, and at Searle Laboratories in Skokie, Illinois.

3. I am a member of the American Association of Pharmaceutical Scientists (AAPS), AAPS Preformulation Focus Group, American Chemical Society and Capsugel Expert System Focus Group, and I am a Registered Pharmacist in the State of Iowa.

4. I am the author of 9 papers and published abstracts in the area of preformulation and formulation of solid dosage pharmaceuticals.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to stable pharmaceutical compositions of Descarboethoxyloratadine (hereafter, "DCL") wherein DCL is in intimate admixture with one or more excipient(s), including, but not limited to, blended, granulated or compressed dosage forms, that avoid the incompatibility between DCL and reactive excipients, such as lactose and other mono- or di-saccharides. I have also reviewed the Office Action in the present case, Serial Number 10/082,685, dated November 5, 2003, as well as the references cited therein, particularly Blaug et al.,[1] Hartauer et al.,[2] and the Handbook of Pharmaceutical Excipients.[3] As a result of my review and general knowledge of the subject area, I make the following analysis:

6. As a person of skill in the art, I take the disclosures of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients as teaching that a primary amine may react with lactose. However, from the teachings of these references, I would expect that a secondary amine, such as DCL, would not interact with lactose and that lactose-containing DCL compositions would be stable. In light of these references, the discovery of the incompatibility of lactose and DCL is unexpected and surprising.

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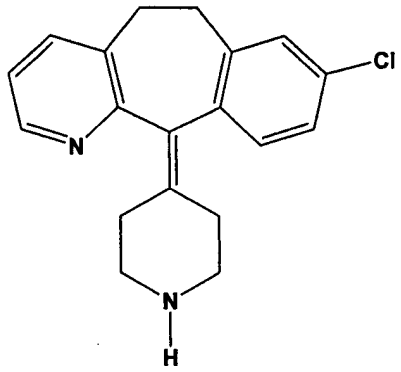
[1] Interaction of Dextroamphetamine Sulfate with Spray-Dried Lactose, J. of Pharma. Sciences, 61 (11), pp. 1770-1775 (1972).
[2] A Comparison of Diffuse Reflectance FT-IR Spectroscopy and DSC in the Characterization of a Drug-Excipient Interaction, Drug. Dev. and Ind. Pharma., 17 (4), pp. 617-630 (1991).
[3] Wade et al., 2nd edition, American Pharma. Assoc. & the Pharma. Press, Royal Pharma. Society of G. Britain, pp. 257-259 (1994).

7. A primary amine is a compound that has a nitrogen atom (N) bound by a covalent bond to only one carbon (C) atom. A secondary amine is a compound that has a nitrogen atom bound by a covalent bond to two carbon atoms. The DCL is a secondary amine since each of its two nitrogen atoms are bound to two carbons as shown below:



The primary and secondary amines represent two distinct species of amine compounds.

8. Blaug et al., in the introductory paragraphs, provides a recitation of early thoughts with respect to the incompatibility of amines (with disregard as to species) and lactose. As Blaug et al. states, early investigators recognized that tablets containing amine salts and lactose discolored (turned brown) slowly on storage and concluded that the discoloration was a result of liberation of free amine by basic lubricants in the formulation. In 1965, however, Duvall et al. concluded that browning did not depend upon liberation of free amine, but that the lactose/amine interaction was predominantly a *primary amine*-carbonyl type of reaction. The investigation conducted by Blaug (1972) confirmed the conclusions of Duvall et al. that the reaction is "a Schiff base-type [reaction] involving the primary amine and the carbonyl group of the sugar." (page 1772, col. 2 and page 1774, col. 1). Thus, Blaug et al. shows that while the early theory for the browning reaction did not account for amine species, subsequent discoveries did, and concludes that lactose/amine incompatibility was the result of an interaction between lactose and a primary amine. Therefore, from the disclosure in Blaug et al., one of skill in the art would not expect a secondary amine, such as DCL, to be reactive with lactose.

9. Hartauer et al. also teaches that the incompatibility between lactose and amines arose as a result of an interaction between lactose and *primary* amines. Hartauer et al. tested aminophylline, a composition comprised of two molecules of theophylline and one molecule of ethylenediamine. This study compared reactivity of lactose with theophylline, a secondary amine, and ethylenediamine, a primary amine. Hartauer et al. found that while theophylline, a secondary amine, did not interact with lactose, ethylenediamine, a primary amine, did. Thus, Hartauer et al teaches that the primary amines are reactive with lactose while the secondary amines are not reactive with lactose. Therefore, the disclosure in Hartauer et al., would make one of skill in the art expect that a secondary amine, such as DCL, would not be reactive with lactose.

10. Similarly, the Handbook of Pharmaceutical Excipients states on page 257 that "a Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products." Thus, the Handbook of Pharmaceutical Excipients does not teach incompatibility of lactose with secondary amines.

11. Furthermore, prior to Applicants discovery, DCL was routinely formulated with lactose (see, e.g., Aberg et al. US Pat No. 5,731,319, Examples 7 & 8). This fact demonstrates that there was no recognition of the fact that DCL, a secondary amine, is incompatible with lactose.

12. Moreover, another secondary amine, astemizole, was commercially available from 1988 until 1999 as HISMANAL® tablets (Janssen Pharmaceutica, Inc.) which, according to the *Physician's Desk Reference*, 50th Ed., Medical Economics Co., Montvale, NJ, p. 1293 (1996), contained in each tablet, 10 mg astemizole and lactose in addition to other ingredients. HISMANAL® was removed from the market in 1999 due to safety concerns and not due to astemizole's incompatibility with lactose.

13. Therefore, it is my conclusion that Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients do not teach or suggest to a person of skill in the art that a secondary amine such as DCL may react with lactose. My conclusion is supported by the fact that at the time of filing of this application, DCL and other secondary amines were routinely formulated together with lactose.

14. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 31st day of March, 2004.

Sharon M. Laughlin

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